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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/537,647	12/28/2005	Koen Vandenbroeck	08830-0344US1	6304

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EXAMINER
HIBBERT, CATHERINE S

ART UNIT	PAPER NUMBER
1636	

NOTIFICATION DATE	DELIVERY MODE
06/24/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/537,647	VANDENBROECK ET AL.	
	Examiner	Art Unit	
	CATHERINE HIBBERT	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 March 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *28-30 and 42-49* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *28-30 and 42-49* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants' submission filed 22 March 2010 is received and entered. This US Application 10/537,647, filed 28 December 2005, is a National Stage entry of PCT/IB03/06404, filed 8 December 2003, which claims foreign priority to UK 02284651, filed 6 December 2002. Claims 1-27 and 31-41 are cancelled. Claims 28-30 are currently amended. Claims 42-49 are newly added. Claims 28-30 and 42-49 are pending and under examination in this action.

The Applicants' Statement of Biological Deposit filed 9/28/2009 in support of the deposit of the vector having accession number ECACC 03120401 and the cell line having the accession number ECACC 03112701 is acknowledged.

Election/Restrictions

Upon careful consideration, the species election requirement of 1/21/2010 is withdrawn herein and therefore the applicants' arguments pertaining to the species election requirement of 1/21/2010 are moot.

Response to Amendment

Any objections and rejections not repeated herein are withdrawn.

The objection to claim 28-30 is withdrawn based on claim amendments.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 28-30 stand rejected and newly added claims 42, 43 and 46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Martens et al in "Protein disulfide isomerase-mediated cell-free assembly of recombinant interleukin-12 p40 homodimers" (Eur. J. Biochem., Vol.267, pages 6679-6683; of record) in view of Barski et al (U.S. Patent No. 6,630,324, filed 7/26/2000, see entire document, of record) and further in view of Graham et al in "Ecdysone-controlled expression of transgenes" (Expert Opinion on Biological Therapy, Vol. 2, June 2002, pages 525-535, of record).

Currently amended base claim 28 is drawn to a method of screening a candidate compound comprising the active method steps of:

(i) incubating a cell culture comprising a cell line transfected with an expression vector comprising DNA encoding a subunit of a dimeric form of interleukin (i.e. p40 β

subunit of IL-12; instant claim 42) under transcriptional control of an ecdysone-inducible promoter with a candidate compound;

(ii) inducing transcription of the dimeric interleukin in the cells of the culture using ecdysone or an ecdysone analog; and

(iii) assaying the cell culture for the presence of secreted interleukin.

New claim 43 is drawn to the method of claim 28 and specifies that the cell line is capable of producing heterodimeric IL-12, the cell line being transfected with an expression vector in which the DNA encodes a p40 subunit of IL-12 and an expression vector in which the DNA encodes a p35 subunit of IL-12.

New claims 46 is drawn to the method of claim 28 and specifies that the cell line comprises cells which are human embryonic kidney cells.

Regarding Claim 28, step (i), Martens et al disclose a method comprising incubating a cell culture comprising cells transfected with a baculovirus expression vector comprising DNA encoding the p40 subunit of the dimeric form of IL-12, under the control of an inducible promoter with a compound of interest.

Regarding Claim 28, step (ii), Martens et al teach inducing transcription of the dimeric p40 IL-12 in the cells of the culture using an inducer (e.g. page 6680, left col., ¶ 1, lines 25-30).

Regarding Claim 28, step (iii) and Claim 29, Martens et al teach assaying the cell culture for the presence of secreted interleukin using a His6-p40 tag using Ni-NTA affinity chromatography (e.g. page 6680, left col., lines 18-22 and Figure 1 and legend).

Regarding Claim 30, Martens et al contemplate probing the cell culture with an antibody specific to a p40 subunit of the dimeric IL-12 (e.g. page 6680, right col., ¶ headed: "p40 ELISA" and "Nonreducing SDS/PAGE and immunoblot").

However, Martens et al differ from the instant invention in that Martens et al fail to teach the use of an ecdysone-inducible promoter expression system.

Barski et al (U.S. Patent No. 6,630,324, filed 7/26/2000, see entire document, or record) teach vectors for inducible protein expression. Barski et al teach that embodiments of the expression vector can comprise an ecdysone-inducible promoter expression system (see column 24, lines 36-50, in particular). Barski et al teach an embodiment in which the expression vector comprises a sequence encoding a p35 and the p40 subunit of IL-12 (see column 62, lines 46-54, in particular). Therefore, Barski et al contemplate host cell lines transfected with at least an expression vector comprising a sequence encoding a p35 and the p40 subunit of IL-12. Barski et al contemplate using their inducible protein expression systems for screening assay tools. In the case of the ecdysone-inducible promoter, the induction would inherently comprise the addition of ecdysone or an ecdysone analog (e.g. see Graham et al entire reference).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have utilized the ecdysone-inducible expression system of Barski *et al* in combination with the method of Martens *et al* because Barski *et al* teach that their vectors encoding a p35 and the p40 subunit of IL-12 were available and were successfully used (e.g. column 62, lines 46-54).

One would have been motivated at the time the invention was made to have utilized the ecdysone-inducible expression system of Barski *et al*. in combination with the method of Martens et al because Graham et al cite numerous benefits to using the ecdysone-inducible expression system, including showing "great potential for use in human gene therapy", stating systems based on insect ecdysone receptors are particularly promising candidates" and are particularly safe for use in animals (see abstract and p.529, right col., ¶ 2, lines 1-8). In addition, both Martens *et al*. and Barski *et al*. are in the same field of endeavor (expression vectors) and both are directed to the same problem sought to be solved (testing compounds that affect the dimerization of subunits of interleukin/IL-12 using expression vector systems).

Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result when utilizing the ecdysone-inducible expression system (as taught by Graham et al and Barski et al) in combination with the standard screening method of Martens et al.

In view of the foregoing, the method of claims 28-30, 42-43 and 46 as a whole, would have been obvious to one of ordinary skill in the art at the time the invention was made. Therefore, the claims are properly rejected under 35 USC *§103(a).*

Response to Arguments

The Applicants' response has been carefully considered but is unpersuasive.

The Applicants' response is to traverse the rejection of claims 28-30 (see Remarks of 9/28/2009), stating:

Applicant disagrees with the Examiner's interpretation of Martens et al. Martens et al. is a paper from the inventors' own group. Applicant respectfully submits that the objectives and subsequent conclusions of the Martens et al. paper are incorrectly characterized by Examiner.

Martens et al. is concerned with two expression systems, a baculovirus expression system which is not inducible and an inducible bacterial expression system. It discusses the utilization of these two different expression systems in two different studies.

As described at page 6681 of Martens et al, the baculovirus expression system is used as a “test system". As this baculovirus expression system was known to successfully express porcine p40, Martens et al utilized the baculovirus expression system to confirm that the addition of a histidine tag to p40 did not prevent expression or dimerization of porcine p40 (see page 6680 column 1). The baculovirus expression system was not inducible and was only used to assess proper, natural, dimerization of secreted p40.

Thus, in contrast to the Examiner's assertion, Martens et al does not "teach a method comprising incubating a cell culture comprising cells transfected with a baculovirus expression vector comprising DNA encoding the p40 subunit of the dimeric form of IL-12, under the control of an inducible promoter with a compound of interest to test the ability of the compound to inhibit dimer assembly".

The bacterial expression vector, inducible with the chemical compound IPTG, discussed by Martens et al, was used to express p40 in a monomeric form which was deposited as an aggregated form in insoluble inclusion bodies (see for example page 6679, first two paragraphs of right hand column). The study by Martens et al utilized the insoluble monomeric p40 expressed by the bacteria to determine a procedure to purify and solubilize the insoluble monomeric p40 from the inclusion bodies. Additional experiments were then undertaken to promote the formation of dimers from the monomeric p40 in vitro using foldases and chaperones (see page 6680, left column, starting at line 31 of Martens et al.).

The aim of the study using the bacterial expression system was to determine conditions to enhance dimer assembly starting from recombinant *E. coli* (bacterial)- produced porcine p40. This contrasts the method of "inhibiting dimer assembly" as described and claimed in the present application. The teaching of Martens et al in relation to "enhancing dimer assembly" completely contrasts the aim of the present application and is completely different in terms of experimental set up, goals/objectives and biological source material used. Even although both focus on IL-12 subunits, the skilled person would not consider Martens et al to teach or suggest a method of inducing p40 expression to test the ability of a

compound to inhibit dimer assembly.

Moreover, "Inhibition" of interleukin dimer assembly according to the present invention is obtained via compounds that act upon the producer cell by changing the secretory pathway of IL-12 subunits, such that these subunits do not dimerize and are not secreted. This is clearly set out in amended claim 28.

In distinct contrast, "enhancement" as described in Martens et al., is based on in vitro experiments in which monomeric unfolded/misfolded IL-12 is provided in dimeric form using buffer compounds and foldases, not using cell-based assays as in the present invention.

Therefore, in contrast to the Examiner's assertion, Martens et al does not teach a method comprising incubating a cell culture comprising cells transfected with a baculovirus expression vector comprising DNA encoding the p40 subunit of the dimeric form of IL-12, under the control of an inducible promoter with a compound of interest to test the ability of the compound to inhibit dimer assembly.

Accordingly, the present methods cannot be considered as a variation of the approach characterized by Examiner as "testing of compounds that affect the dimerization of subunits of IL-12 using expression vector systems". One cannot predict the method or approach needed to inhibit IL-12, when starting from the methods used to enhance IL-12 dimers as described and taught in Martens et al.

With respect to the Examiner's statements regarding the relevance of Barski et al. (office action, bottom of page 4 and in page 5), Applicants submit these comments are only partially correct. There is no evidence to support the Examiner's statement that "Barski et al teach that their vectors encoding a p35 and the p40 subunit were available and were successfully used". In Barski, the recombinant DNA vector, based on the aldehyde reductase gene, (see claim 9 of the Barski patent document) is available, but all the DNA sequences provided in the Barski patent appear to constitute fragments that function as bidirectional promoters. The vector described in the Barski patent contains a bidirectional promoter to regulate expression of two separate genes. Further, Barski provides examples of where co-expression of two genes could be conceived to form functional heterodimers. However, the prior art document does not provide evidence of DNA sequences coding for p40 or p35, nor does it provide evidence that vectors encoding p35 and p40 were either available or successfully used. All DNA sequences provided in the Barski patent (SEQ ID NO.19 ....NO.31, page 61) represent fragments of the aldehyde reductase promoter in which no identification of p40 or p35 in these DNA sequences can be made.

> In the last paragraph of page 5 of the office action, Examiner outlines the reasons why it would have been allegedly obvious at the time of the invention to utilize the ecdysone-inducible expression system of Barski et al in the method of Martens et al. As already outlined above, the purpose of Martens et al. is to reconstitute dimeric (p40) starting from solubilized bacterial inclusion bodies, not to test compounds inhibiting dimerization of IL-12 subunits.
>
> There would have been no point in using the ecdysone inducible expression system of Barski in the work performed by Martens et al, as the aim of Martens was to study the parameters that affect refolding of p40, starting from p40 purified from inclusion bodies. The Martens et al paper was precisely and specifically intended to define conditions supporting formation of dimeric p40 forms in vitro by means of enzymatic (foldase-based) methods starting from monomeric p40. In addition, there appears to be no evidence in the Barski patent to contemplate testing compounds that affect dimerization of subunits of IL-12 using expression vector systems.

In conclusion, Applicants' argue that the "Examiner has misinterpreted the teaching of both Martens et al., and Barski et al" and thus, "with knowledge of the present invention, the Examiner has incorrectly combined the cited teachings to reach the incorrect conclusion that the invention of claim 28 would have been obvious".

The Applicants' arguments have been carefully considered but are unpersuasive. In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

In response to applicant's argument that there is no teaching, suggestion, or motivation to combine the references, the examiner recognizes that obviousness may be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988), *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992), and *KSR International Co. v. Teleflex, Inc.*, 550 U.S. 398, 82 USPQ2d 1385 (2007). In this case, one would have been motivated at the time the invention was made to have utilized the ecdysone-inducible expression system of Barski *et al*. in combination with the method of Martens et al because Graham et al cite numerous benefits to using the ecdysone-inducible expression system, including showing "great potential for use in human gene therapy", stating systems based on insect ecdysone receptors are particularly promising candidates" and are particularly safe for use in animals (see abstract and p.529, right col., ¶ 2, lines 1-8). In addition, both Martens *et al*. and Barski *et al*. are in the same field of endeavor (expression vectors) and both are directed to the same problem sought to be solved (testing compounds that affect the dimerization of subunits of interleukin/IL-12 using expression vector systems).

New ground of rejection

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 28-30 and 42-49 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Currently amended Claim 28 recites the limitation "the dimeric interleukin" in line 8. There is insufficient antecedent basis for this limitation in the claim because although the claim now recites “a subunit of a dimeric form of interleukin” there is no prior reference to “a dimeric interleukin”.

Claims 29-30 and 42-49 are indefinite insofar as they depend from Claim 28.

Conclusion

No claims allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to CATHERINE HIBBERT whose telephone number is (571)270-3053. The examiner can normally be reached on M-F 8AM-5PM, EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.
/NANCY VOGEL/
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